JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PHARMACEUTICAL SUSPENSIONS AN UPDATED REVIEW FOR PATIENT COMPLIANCE WITH ORAL DOSAGE FORMS

Mr. Malunjkar D.D (Department of Pharmaceutics) [1], **Dr. Maru A.D** (Department of Pharmaceutics) [2], **Dr. Surana S.S** (Department of Pharmacognosy) [3], **Miss. Pagar P.K** (Department of Pharmaceutics) [4]
Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Tal-Kalwan, Dist-Nashik (423501) Maharashtra, India

Abstract
Oral dosage forms are mostly acceptable due to its patient compliance and easy administration of the drugs. Due to low coast and easily administration of the drugs oral suspension is mostly preferable dosage form in case of pediatric and geriatric patients and other age group peoples. Due to stability and greater acceptability of liquid it has few benefits over ordinary dosage forms. Not all the dosage forms are formulated in form of suspension, but due to other dosage forms oral suspension are ideal and alternative dosage form for children's having difficulties in swallowing of tablets or capsules. Unpleasant taste of drugs is usually masked by oral suspensions and some drugs are chemically stable in case in suspension dosage form compare to solutions. Chemical stability of drugs is also increase in case of suspensions dosage form. Drug have higher dose in dosage form which usually incorporated into suspension. The present review focus on the various aspects of oral suspensions such as its classification, advantages and disadvantages, Reason behind formulating, important considerations in formulation, formulating aspects, IPQC tests, Packaging and labelling.
Keywords: Oral suspension, Suspending agents, Zeta potential, Stability, Dispersed.

Introduction

A poorly soluble active ingredient has long been administered in the suspension dose form for a wide range of therapeutic purposes. The development of stable suspensions for the extent of the drug product's shelf life is still difficult on several levels. It's critical to have a solid grasp of the foundations of dispersion systems in order to creation of an appropriate pharmacological suspension. The process of creating a suspension dosage form is quite difficult. It is crucial to choose the right excipients (surfactants, agents that impart viscosity, etc.) (Kulshreshtha et al., 2009).The finished drug product dosage form's particle size distribution is a key factor that profoundly affects the product's pharmacokinetics and bioavailability. To appropriately characterize the suspension, suitable analytical tools and techniques (such as chromatographs, viscometers, particle size analyzers, etc.) must be used (Goins et al., 2002).Clinical studies are necessary to validate the safety and effectiveness of the drug product, as per regulatory organizations around the world. Based on the regulatory requirements, this entire development activity should result in a regulatory file (Nahata et al., 1999). Pharmaceutical Suspensions, From Formulation Development to Manufacturing adopts an organization culture that is consistent with the development methodology that is frequently employed in the pharmaceutical sector (Grießmann et al., 2007).For the study of the suspension we have to know the disperse system It have at least two phases the dispersed material, also known as the internal phase, and the continuous phase, also known as the exterior phase. Dispersions are typically divided into molecular dispersions, colloidal dispersions, and coarse dispersions based on the particle size of the dispersed phase (Dickinson et al., 2003). Particles dispersed in molecular dispersions are less than 1.0 nm in size. Particle sizes in colloidal dispersions range from 1 nm to 1 m. Another type of colloidal dispersion is a microemulsion, while others include nanoparticles and microspheres. Particles in coarse dispersions, which include suspensions and emulsions, are larger than 1 m (Matveenko et al., 2011).

Suspension

A heterogeneous mixture is referred to as a suspension if the solid particles are dispersed throughout the liquid without actually dissolving in it.

It is a homogeneous mixture of particles that are visible to the human eye and have a diameter bigger than 1000 nm is referred to as a suspension (Viveksarathi et al., 2012). It is a heterogeneous system consisting solid particles are dispersed in liquid medium (Pharmacopoeia et al., 1996).

Classification of suspensions

- On the basis of general classes
  a. Oral Suspensions
     These are the preparations that administered by oral route e.g.Paracetamol suspension.
  b. Topical suspensions
     These are the preparations that administered by topical route of administration via epidermal layer of skin e.g. calamine lotion.
  c. Parenteral suspension
     These are the preparations that administered by intravenous or intramuscular route via syringe e.g. Triamcinolone Acetonide injectable suspension.
  d. Suspension creams
     These are the preparations that applied on a skin e.g. Face creams.
- On the basis of proportion of solid particles
  a. Concentrated suspension
     These are the suspension contains Contain 2to 10 %W/V Solid e.g. Zinc oxide suspension.
  b. Diluted suspensions
     These are the suspension Contains 50%W/V Solid e.g. Cortisone acetate.
- On the basis of Electro kinetic nature of solid particles
  a. Flocculated suspensions
     These are the suspension that forms the (Flocs) or large clusters when flocculating substance is adding into them e.g.Hydrophilic polymers and electrolytes.
  b. Deflocculated suspensions
     These are the suspension that does not form the (Flocs) or large clusters.
- On the basis of size of solid particles
  a. Colloidal suspension
     These are the suspensions having size range < 1 micron, suspension.
  b. Coarse suspension
     These are the suspensions having size range >1 micron.
  c. Nano suspension
     These are the suspensions having size range 10ng **(**Kumar et al., 2016).

Oral suspensions

An oral suspension is a finished pharmaceutical product with the drug substance as active component. It consists of the drug substance in a dose form suspended in a liquid for oral administration. Oral Suspension is a finished pharmaceutical preparation that includes the drug substance as an active component. It consists of the drug substance dosage formulation suspended in a liquid for oral administration (Pons et al., 1997).

Advantages of oral suspensions

- Improves the physicochemical stability of certain drugs e.g. Procaine penicillin G.
- Easy delivery of low soluble therapeutic agents.
- Oral suspension increases the bioavailability of oral dosage form.
- Easy to transportation.
- Duration of action of this type of suspension is controlled (Kumar et al., 2016).

Disadvantages of oral suspensions

- Oral suspensions are fundamentally unstable.
- Accurate amount of dose cannot be possible.
- Difficulty at the time of administration in case of pediatric patients (Bardeskar et al., 2014).
- Difficulty in the formulation.

Reason to formulation of oral suspension

If the drug material is insoluble in the liquid medium in that condition we move towards the oral suspensions (Bardeskar et al., 2014).For increasing stability of drug material which is unstable in solid state in that condition we move towards the suspension dosage form. For sustain release of the drug suspension is preferable dosage form (Bruns et al., 2018).

Important considerations for formulation of oral suspensions

Formulation of pharmaceutical suspensions requires knowledge of properties both dispersed phase and dispersion medium. Suspension formulation materials should be carefully selected with route considerations in mind. Administration, intended use, possible side effects less than most important factor to consider when formulating pharmaceutical suspensions (Ribeiro et al ., 2015).

- Nature of suspended material

  The interfacial properties of suspended solids are an important consideration during suspension formulation. Particles with low interfacial tension are easily wetted by water and can be easily suspended (Kulshreshtha et al., 2009). However, particles of high interfacial tension materials are not easily wetted. Suspension of such materials is usually accomplished through the use of surfactants. Surfactants increase the wettability of particles by lowering their surface tension (Pabst et al., 2004).
- Viscosity of the dispersion medium

  A higher viscosity dispersion medium has the advantage of slower sedimentation. However, other desirable properties such as injectability for parenteral suspensions, spreadability for topical suspensions, and ease of administration for oral suspensions may be compromised (Weiner et al., 1986). Shear thinning is highly desirable, so when minimal shear is present, suspensions are very viscous during storage, resulting in slow settling, low viscosity after agitation (high shear), and bottle Ease of pouring from is improved (Kulshreshtha et al., 2009).
- Size of suspended particles

  A decrease in particle size leads to a decrease in the settling velocity of suspended particles, as described by Stoke's law (Kulshreshtha et al., 2009). Particle size reduction can be achieved by methods such as milling, sieving, and milling. Particle size also affects the rate and extent of drug absorption, dissolution, and bio-distribution. However, reducing the particle size beyond certain limits can result in the formation of compact cakes upon sedimentation (Gallardo et al., 2000).

Theoretical considerations in development of oral suspension

- **Interfacial Properties of solid particles**

  The solid phase is still present in pharmaceutical suspensions as finely divided particles in the dispersion medium. As a result, the formation involves a lot of interface, which impacts the stability of suspension preparations (Gallardo et al., 2000). Therefore, the interfacial properties are crucial in changing the physical parameters of dispersion. Surface free energy and surface potential are the two most significant interfacial properties (Garcell et al., 2017).

- **Surface Free Energy**

  Finely divided solid materials typically have a big surface area and a large amount of free energy on the surface. The following is an expression for the relationship between surface free energy and surface area:

  $$\Delta G=\boldsymbol{\gamma}\Delta A$$

  Where ΔG is the increase in surface area, and it is the interfacial tension among the solid particles and the dispersion medium. The smaller the ΔG is, the greater the thermodynamically stable is the suspension (Osorio et al., 2017). Therefore, a system with very fine particles is thermodynamically volatile due to excessive overall surface area. Thus, the system has a tendency to agglomerate if less the surface area and thereby the increasing free energy. Surface free energy will also be decreased to keep away from the agglomeration of particles, which may be done through reducing interfacial energy. When a wetting agent is transferred to the suspension formulation, it is adsorbed on the interface. This will results a reduction of the interfacial tension, making the system more stable (Reiner et al., 1990).

- **Electric Double Layer**

A major component of the process governing the electrostatic stability of colloids is the phenomenon known as an electric double layer. When negatively charged ions from the dispersion media are adsorbed on the particle surface, colloidal particles acquire a negative electric charge (Reiner et al., 1990).The positive counterions around a negatively charged particle are drawn to it. Are shown in the below figure 1.

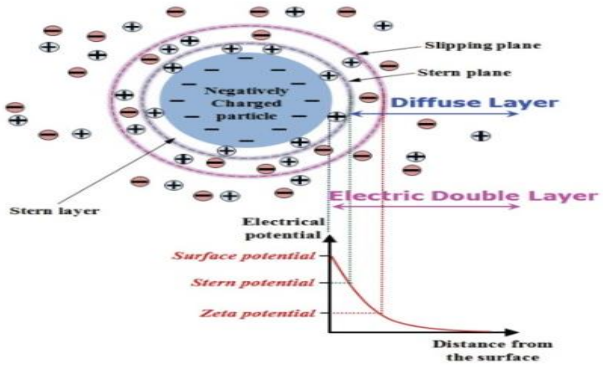

Figure1. Electric Double Layer

The area around a particle of dispersed phase, containing the ions adsorbed on the particle surface and a film of the countercharged dispersion medium, is referred to as an electric double layer. Electrically speaking, the electric double layer is inert.

Electric double layer contains three parts;
1. Surface charge
Adsorbed charged ions (mainly negative) on the surface of the particle.
2. Stern layer
Counterions (charged in the opposite direction from the particle surface charge), drawn to the particle surface and tightly bound to the electrostatic force.
3. Diffusion Layer
A film of the dispersion medium (solvent) next to the particle is referred to as a diffuse layer. Free ions with a larger concentration of the counterions can be found in the diffuse layer. The charged particle's electrostatic force has an impact on the ions in the diffuse layer.
On the particle surface, the electrical potential within the electric double layer reaches its highest value (Stern layer). The potential decreases with increasing distance from the surface and zeros out at the electric double layer boundary.
A coating of the surrounding liquid adheres to a colloidal particle as it moves in the dispersion medium. The sliding plane is the name given to this layer's boundary (shear plane). Zeta potential, a crucial component of the theory of colloidal particle interaction, is the measurement of the electric potential at the sliding plane (Hou et al., 2007).

- **Zeta potential**

An inner region (Stern layer) where the ions are tightly bonded and an outer (diffuse) region where they are less closely bound make up the liquid layer that surrounds the particle. There is a hypothetical border within the diffuse layer where the ions and particles come together to form a stable entity (Hou et al., 2007).Ions within the border move a particle when it moves (for instance, because of gravity). Beyond the barrier, the ions remain with the bulk dispersant (Larsson et al., 2012).The zeta potential is present at this border (surface of hydrodynamic shear).Are in following figure.2

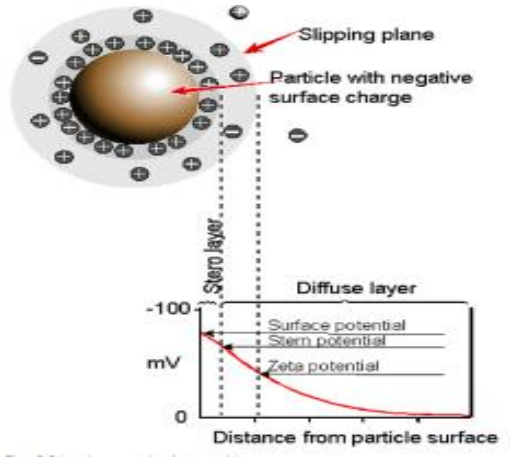

Figure2. Zeta potential

The colloidal system's potential stability is indicated by the zeta potential's magnitude. The tendency for the particles to attract each other and come together will be absent if all the particles in suspension have a strong negative or positive zeta potential. There won't be any force to stop the particles from combining and flocculating, though, if the particles have low zeta potential levels.

It is customary to draw the border between stable and unstable suspensions at either +30 or -30 mV. Generally, stable particles are those with zeta potentials greater than or equal to +30 mV or greater than -30 mV (Júnior et al., 2014). Even though they are dispersed, particles with a density larger than the dispersant will eventually settle and create a closely packed bed (i.e. a hard cake).

The zeta potential of a particle must therefore include the definition of the nature of the dispersion as well, if the zeta potential of different materials is to be compared, as the zeta potential depends on the nature of the dispersant as well as the surface (Greenwood et al., 2003).

The factors like pH, Conductivity, Concentration of formulation component.

- **Wetting of particles**

An important phase in the manufacturing process that requires further thought is the first dispersion of an insoluble powder in a medium. Occasionally, especially during large-scale operations, the vehicle will receive powder additions by dusting the liquid's surface. Due to pollutants such an adsorbed layer of air, minuscule amounts of oil, and other contaminants, it is frequently challenging to spread the powder. Despite having a high density, the powder does not readily wet and floats on the liquid's surface. Due to entrained air, finely powdered particles are especially vulnerable to this effect and do not become moist even when driven beneath the surface of the suspending medium (Bossler et al., 2016). It is simple to determine a powder's wettability by looking at the contact angle it forms with the liquid's surface. When the particles are fully out of the liquid and floating, the angle is roughly 90° (Sun et al 2002).

One that dives obviously has no contact angle, while one that floats low in the liquid has a smaller angle. The term "hydrophobic" refers to a property of powders such as sulphur, charcoal, and magnesium stearate that prevents water from quickly wetting them and results in a large contact angle. Hydrophilic powders are those that, when free of impurities that have been adsorbed, are easily wettable by water (Bossler et al., 2016). The latter category includes talc, magnesium carbonate, and zinc oxide.

When making a suspension, surfactants are very helpful in lowering the interfacial tension between solid particles and a vehicle. The decreasing interfacial tension lowers the advance contact angle, displaces air from the surface of the particles, and encourages wetting and deflocculation (Sun et al., 2002).

- **DLVO Theory**

The zeta potential is utilized in DLVO theory, a colloidal dispersion stability theory, to explain why a repulsive force develops as two particles get close to one another and their ionic atmospheres start to overlap. Based on this idea, electrical double layer forces and Van der Waals forces both have an effect on colloidal stability (Ninham et al., 1999).

A theory of colloidal stability was created by Derjaguin, Landau, Vervey, and Overbeek (DLVO), and it presently serves as the basis for our knowledge of colloidal particle interactions and aggregation behaviour. This theory is also utilized to explain particle deposition on planar substrates and forces acting between interfaces (Trefalt et al., 2014). In order to explain forces between planar substrates, such as thin liquid sheets, the same approach is also applied. The main concepts were firstly discovered by Boris Derjaguin, expanded

upon in a seminal piece co-authored with Lev Landau, and then more generally disseminated in a book by Evert Verwey and Jan Overbeek (Ninham et al., 1999).The theory was initially developed for a symmetric system with two identical interfaces, which corresponds to the scenario of an accumulation of similar particles (homoaggregation). Later, this idea was expanded to include the two distinct interfaces (asymmetric system) and the aggregation of various particles (heteroaggregation) (Adamczyk et al., 1999).This procedure is comparable to the deposition of particles on a flat substrate in the restricting case of significant size disparity between the particles.

The figure below provides an illustration of these procedures.

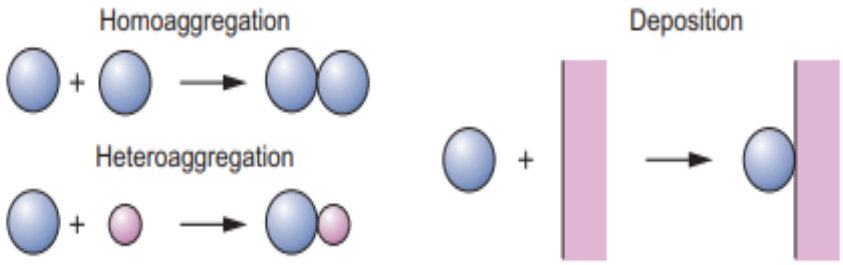

Figure3. Homoaggregation in particles

- **Flocculation**

Small particles in suspension can be made to aggregate by a process called flocculation, which produces enormous clusters (flocs) that are much easier to separate than the original particles(Gregory et al., 1989). The method is widely used in a variety of industrial applications.

In many industrial applications, including biotechnology, mineral processing, papermaking, water and wastewater treatment, and others, flocculation is a common procedure. It mostly depends on the attachment and collision of particles in a suspension. This results in the formation of particle aggregates (flocs) that are considerably larger than the initial (primary) particles, allowing for easier physical separation. Aggregation is the general word for this procedure (Bratby et al., 1980).

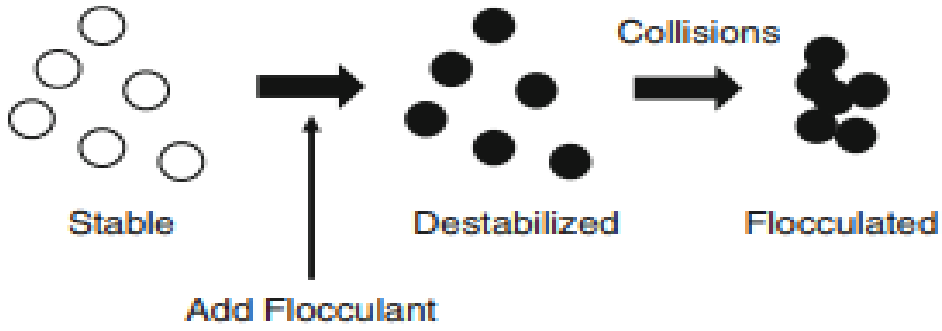

Figure4. Flocculation in particles

- **Deflocculation**

In the ceramic, paper, and dye industries, reducing viscosity by adding a tiny amount of suitable electrolyte to suspensions to facilitate transport, agitation, and other mechanical operations the term for this procedure is deflocculation (Gregory et al., 1989).

A suspension that has not undergone flocculation is said to be deflocculated. Particles are distinct things that exist; Sedimentation happens slowly, Sediment built up gradually. As the repelling interactions between the particles are overcome, sediment becomes extremely tightly packed, forming a hard cake that is challenging to redisperse (Landrou et al., 2018).

Formulation of suspensions

A variety of things need to be considered while creating a suspension formula. First, a choice must be made regarding whether to evolve a flocculated or non-flocculated system. Second, it's crucial to make sure that the particles from the disperse phase are evenly dispersed in the continuous phase (Kumar et al., 2016) .The choice of suspending agents, dispersants, organoleptic additives, and preservatives must then be made in order to achieve a good suspension.
The use of the products, the facilities for preparation and the length of product storage all affect the choice of an acceptable suspending agent.

List of commonly used suspending agents used in formulation of oral suspensions

- Alginates
- Methylcellulose
- Hydroxyethylcellulose
- Carboxymethylcellulose
- Sodium Carboxymethylcellulose
- Microcrystalline cellulose
- Acacia
- Tragacanth
- Xanthan gum
- Gelatin

Mostly used suspending agents in oral suspensions

- **Alginates**

  In the pharmaceutical industry, sodium alginates are commonly utilized as gel-forming agents in conjunction with divalent metal ions like calcium or as suspending and thickening agents in suspensions, water-miscible gels, lotions, and creams. Pharmaceutical-grade alginates are produced using various botanical sources, seaweed collecting locations, harvesting seasons, plant sections, and processing techniques. Tragacanth and alginate salts have a similar suspending effect. When heated over 60^0C, the viscosity of the alginate solution decreases. As result of depolymerization, the viscosity of the solution is maximum while it is fresh; after that, it steadily declines and becomes constant after 24 hours. At pH values between 5 and 9, the highest viscosity is seen. In food sector and as bulk laxative, alginate is utilized at lower concentrations to minimize the problem of viscosity due to its strong thickening impact (Sutherland et al., 1991).

- **Methylcellulose**

  Methylcellulose is a cellulose methyl ester in which some of the hydroxyl groups have been methylated. Depending on the degree of polymerization (between 50 and 1000) and molecular weights, it comes in a variety of grades (in the range 10 000 – 220 000 Da). Methylcellulose of the pharmaceutical grade is offered as a white powder or granular substance. It basically has no flavor or smell. A cellulose methyl ester with a range of chain lengths and levels of methylation is known as methylcellulose. It is one of the most frequently used cellulose ethers in industry and is produced by reacting methyl chloride with alkali cellulose. Methylcellulose, like other cellulose ethers, is made up of glucose units (more than 10,000) that are connected by β(1-4)-glycosidic linkages and contains the polymeric backbone of cellulose, a naturally occurring linear polymer glucan. The percentage of hydroxyl groups replaced by methyl ether residues ranges from 27 to 32%, and the degree of polymerization is between 50 and 1000 (Marques-Marinho et al., 2013).The molecular weights (number average) fall between 10,000 and 220,000 Da. The average number of methoxyl groups that are joined to each anhydroglucose unit throughout the chain is used to define the degree of substitution of methylcellulose. Methylcellulose's physical characteristics, including its solubility, viscosity in aqueous solution, and glass transition temperature, are significantly influenced by the degree of replacement. Methylcellulose of the pharmaceutical grade is offered as a white, fibrous powder or granules. It has no taste and is almost tasteless (Abu-Jdayil et al., 2014). It should be labelled (for a 2% w/v aqueous solution) to specify the type of viscosity it has.

- **Hydroxyethylcellulose**

  Hydroxyethylcellulose, often known as HEC, is a non-ionic, water-soluble polymer thickening agent and suspending agent that is extremely effective, easily distributed, and utilized for stability in addition to thickening (Marques-Marinho et al., 2013). This product makes formulating very simple because the particles

have been blocked. Its brand is Natrosol HHR, a very effective product, and when the particles are put to water, they should easily disperse without lumping (Guo et al., 1998).

- **Carboxymethylcellulose**

The most promising cellulose derivative is carboxymethyl cellulose (CMC). It is widely used in a variety of advanced application fields, such as the food, paper, textile, and pharmaceutical industries, biomedical engineering, wastewater treatment, energy production and storage, and so on (Marques-Marinho et al., 2013). This is due to its distinctive surface properties, mechanical strength, tunable hydrophilicity, viscous properties, availability and abundance of raw materials, low-cost synthesis process, and likewise many opposing aspects. An anionic, water-soluble derivative of cellulose, a linear polysaccharide of anhydro-glucose, is carboxymethyl cellulose (CMC).1,4-Glycosidic linkages link the repeating units together. Only a few anionic carboxymethyl groups (i.e., -CH2COOH) in the CMC structure, which replace some of the hydroxyl groups present in the pure cellulose infrastructure, are the primary molecular difference between CMC and cellulose. The synthesis of CMC began in 1918. However, the first depiction of the commercial manufacture of these crucial polymeric materials was made in Germany in the early 1920s (Rahman et al., 2021).

- **Sodium Carboxymethylcellulose**

The sodium salt of the carboxy-methyl ether of cellulose, known as sodium carboxymethyl cellulose (CMC), dissolves in water and creates a transparent colloidal solution. It is a hygroscopic substance with the capacity to absorb more than 50% of water when the relative humidity is high. It can also be employed as a natural polymeric derivative in the textile, food, and detergent sectors. (Varshney et al., 2006) Palladized iron nanoparticles can be stabilised using CMC, and these nanoparticles can then be employed to dichlorinate contaminated subsurfaces. In order to create a composite with a crystalline nanofibril for the creation of long-lasting bio-based polymers, it can also be employed as a polymeric matrix. To make sodium ion batteries, CMC can also bond to a hard carbon electrode (Solberg et al., 1977).

- **Microcrystalline cellulose**

MCC is a naturally occurring compound made from cellulose that has been refined and partially depolymerized. Alpha cellulose is traditionally treated with an excessive amount of mineral acids to prepare it. Alpha cellulose is made up of microfibrils that have paracrystalline and crystalline phases at the nanometer scale (Battista et al., 1962).

The crystalline sections are made up of tightly packed microcrystal bundles in a strict linear structure, whereas the paracrystalline area is an amorphous mass of cellulose chains. Because of van der Waals interactions and hydrogen bonds, the crystalline areas are known as cellulose crystallites and are created by cellulose chains. These crystallites' diameter is comparable to that of cellulose microfibrils in size.

Currently, a variety of different cellulosic sources are used to create MCC. Wood and cotton are by far the most significant feedstocks used in the production of MCC because they are the primary industrial sources of cellulosic fibres (Azani et al., 2020).

- **Acacia**

Acacia, commonly called as gum Arabic, serves as an emulsifier, stabilizing agent, suspending agent, tablet binder, and viscosity-increasing agent in the pharmaceutical sector. The dried sticky exudate of Acacia Senegal and other Acacia species (family Leguminosae) is known as acacia and is made as a syrup and mucilage. Additionally, it is employed in the culinary arts to give processed dishes body and texture.

It is a complex polysaccharide made up of mixed calcium, magnesium, and potassium salts that are branching neutral to acidic aggregates (Marques-Marinho et al., 2013). The 1,3-linked D-galactopyranosyl unit backbone is made up of two to five additional 1,3-linked D-galactopyranosyl units. The characteristics of Acacia vary significantly according on the source. The pharmaceutical excipient grade is typically provided in the form of flakes, tears, granules, powders, or spray-dried powders that are white or yellowish-white in colour. It has no smell and a tasteless (Femi-Oyewo et al., 2004).

- **Tragacanth**

A natural gum called Tragacanth is created from the dried sap of Middle Eastern bean species of the Astragalus genus. It is a thick mixture of polysaccharides that is water soluble, flavourless, and odourless.

Tragacanth gives a solution thixotrophy (forms pseudoplastic solutions) (Kulkarni et al., 2015). Due to how long it takes for the solution to fully hydrate, the solution's maximal viscosity is only reached after several days.

Tragacanth is stable at pH range of 4 to 8, it's thickens more effectively than acacia, as a thickening, stabilizer, emulsifier, and suspending agent, and Tragacanth is used (Nejatian et al., 2020).

- **Xanthan gum**

Xanthan gum is a polysaccharide secreted by the bacterium Xanthomonas campestris. It is composed of pentasaccharide repeat units, comprising glucose, mannose, and glucuronic acid in the molar ratio 2:2:1.Rheology modifier as a stabilizer (in cosmetic products, e.g, to preventingredients from separating (Nejatian et al., 2020). Hot and cold water soluble gives neutral pH, pseudoplastic (shear thinning) solutions. It is very stable under a wide range of temperatures and pH (3–12) and Xanthan gum is widely used as a suspending agent in liquid formulations (Emam-Djomeh et al., 2019).

- **Gelatin**

Gelatin is a transparent, flavourless, and colourless food additive that is often made from collagen extracted from animal body parts. When dry, it is brittle; when wet, it becomes rubbery. After being hydrolyzed, collagen can alternatively be referred to as hydrolyzed collagen, collagen hydrolysate, hydrolyzed gelatin, and collagen peptides (Eraga et al., 2014). It frequently serves as a gelling ingredient in a variety of products, including food, drinks, medicines, vitamin or drug capsules, photographic films, papers, and cosmetics.

Gelatin is a transparent, flavourless, and colourless food additive that is often made from collagen extracted from animal body parts. When dry, it is brittle; when wet, it becomes rubbery. After being hydrolyzed, collagen can alternatively be referred to as hydrolyzed collagen, collagen hydrolysate, hydrolyzed gelatine, and collagen peptides. It frequently serves as a gelling ingredient in a variety of products, including food, drinks, medicines, vitamin or drug capsules, photographic films, papers, and cosmetics (Harsha et al., 2013).

Components of oral suspensions

Table1. Components of oral suspensions

Components	Function
API	Active drug substances.
Wetting agents	They are added to disperse solids in Continous liquid phase.
Flocculating agents	They are added to floc the drug particles.
Thickeners	They are added to increase the viscosity of suspension.
Antioxidants	They are added to prevent the oxidation in suspensions.
Antifoaming agents	They are added to prevent the foam in suspensions.
Buffers and PH adjusting agents	They are added to stabilize the suspension to a desired PH range.
Colouring agents	They are added to impart desired colour to suspension and improve elegance.
Preservatives	They are added to prevent microbial growth.

- **Active pharmaceutical Ingredient**

Pharmaceutical active ingredient suspensions can be based on hydrophilic or hydrophobic liquids, with the active ingredient being evenly and finely dispersed throughout. The goal is to evenly distribute the API throughout the solvent and to long-term stability against separation. The particle size reduction of an API suspension would be another area. To reach the desired location, some active substances must fall within a specified range of particle size (i.e. cells, skin). Using FrymaKoruma/ProXES technology, problems like as

particle size reduction to the nanoscale, processing under ATEX conditions, or precise feeding of small API quantities with controlled homogenising can be solved (Pons et al., 1997).

- **Wetting agents**
  Wetting agents are used to enhance the liquid vehicle's flow across the particle surface, which enhances the uniformity of drug particle distribution throughout the formulation. Examples include sorbitan esters, polysorbates, and others (Karnok et al., 2004).

- **Flocculating agents**
  These electrolytes are neutral and can keep suspended solids from caking. Sodium or potassium chloride, aluminum chloride, calcium salts, citrates, etc. are some examples of flocculating agents used in pharmaceutical solution (often at concentrations 0.01 - 1.00%) (Brostow et al., 2007).

- **Thickeners**
  They are added to increase the viscosity of suspension. Excipients that increase the viscosity during formulating of suspensions, Proteins (eggs, collagen, gelatin, blood albumin), polysaccharides (starches, vegetable gums, and pectin), and fats (butter, oil and lards) are examples (Taylor et al., 1974).

- **Antioxidants**
  Antioxidants are necessary in certain pharmaceutical suspensions to improve the therapeutic agent's chemical stability, which might be affected by oxidation. Thiourea, butyl hydroxy toluene (BHT), tocopherols, ascorbic acid, sodium bisulphates are the examples (Aliabadi et al., 2008).

- **Antifoaming agents**
  They are added to prevent the foam in suspensions. Excipients that stops foam when making suspensions or reconstituting powder for suspension. Simethicone, organic phosphates, alcohols, paraffin oils, stearates, and glycols are a few examples (Mark et al., 2013).

- **Buffers and PH adjusting agents**
  Agents that are added to suspensions to regulate potential pH variations in formulations are known as buffering agents or pH modifiers. Pharmaceutical suspensions frequently use the buffers citrates and phosphates. While phosphate buffers are utilized in the pH range of 7 to 8, citrate buffers are used to stabilize suspensions in the range of 3 to 5 (Aliabadi et al., 2008).

- **Colouring agents**
  These are agents gives the finished product a more appealing appearance. The choice of flavor is typically linked to the choice of colourant, and these decisions are also influenced by factors related to the patient population, including age group, location, and therapeutic need. For pediatric formulations, a red colourant is typically combined with strawberry flavor (Šuleková et al., 2017).

- **Preservatives**
  Aqueous suspensions frequently have preservatives added to them in order to protect them against microbiological contamination. Preservatives such parabens, alcohol, glycerin, propylene glycol, and sorbates are frequently employed in pharmaceutical solutions (Sengupta et al., 2021).

In-Process Quality Control (Ipqc) test during formulation of oral of Suspensions

IPQC stands for in process quality control. These tests are performed during the manufacturing process is being finished. Monitoring and, if necessary, modifying the production process to conform to the standards is the purpose of in-process controls.
In Process quality control is the process of keeping an eye on key elements of the production process to guarantee the quality of the finished product and to provide the appropriate guidance if any discrepancies are discovered. To guarantee that a predictable portion of each output cycle falls within the acceptable standard range, quality control and production employees establish and document rules for in-process manufacturing (Kumar et al., 2016).

Following are the IPQC test that are consider during the formulation of dosage form

- **Identity test**
  Identity tests are qualitative chemical techniques used to confirm the compound's true presence. Such as precipitation or color formation
- **Purity test**
  The level of all observable and significant impurities and contaminants in the pharmacological compounds is estimated. Test for suspension is acidity, and alkalinity.
- **Quality test**
  These examine the physical procedures that accurately determine drug's qualities and properties. Such as absorbance or refractive index
- **Potency test**
  This test investigates the quality of active ingredient in formulation.
- **Biological and microbiological tests**
  It includes tests for safety, toxicity, pyrogenicity, sterility, antiseptic activities, and the efficacy of antimicrobial preservatives in macro and micro biological ways (Ghorpade et al., nd).

Purpose of IPQC tests (Kumar et al., 2016)

- To reduce the human error during formulation.
- To check an equipment during formulation.
- To improve the quality of manufacturing.
- To detect the abnormality immediately.

IPQC test for suspensions (Shirisha et al., 2014)

- Appearance
  Color, odor, and taste (The product is examined for colour uniformity and the absence of air bubbles)
- Clarity
- Disperse Phase Particle Size
- Rheology
- Water Quality Control
- Sedimentation Volume
- Sedimentation Rate
- Drug content
- Zeta potential
- stability test
- Redispersibility
- pH of various vehicles before and after mixing Compatibility of product and container/closure

Packaging of oral Suspensions

An inventive packing method designed specifically to safeguard delicate items during transportation is suspension packaging. In order to ensure correct mixing, pharmaceutical suspensions for oral use are typically packed in wide mouth containers with enough space above the liquid. Glass ampoules or glass vials are used to package parenteral suspensions.

Ideal Requirements of Packaging Material

- Packaging material should be should be inert, it not react with drug substance.
- Packaging material should be protecting the product from light, air, and other contamination.
- Packaging material should be cheap and easily available.
- Packaging material should be delivering the product during the transportation (Lockhart et al., 1996).

Materials used for Packaging of oral suspensions

- **Glass**

Due to qualities like recycling, reuse, and neutral reactivity, glass is often used as a packing material. It prevents contamination and long-term food and beverage preservation. For instance, beer is preserved by being kept in dark glass bottles. Additionally, because glass has a neutral nature and does not react, this packaging is utilised in the chemical industry. Interactive design is a key component of glass packaging that draws customers in (Gahleitner et al., 2019).

Glass jars, lids, containers, and bottles come in a variety of sizes, styles, and colours to suit different needs. Food, drinks, chemicals, medications, cosmetics, and other products are frequently packaged in glass. Glass ampoules, glass bottles, glass lids, and glass stoppers are the product segments that make up the worldwide glass packaging market. The applications market is divided into categories such as food packaging, packaging for alcoholic and non-alcoholic beverages, packaging for pharmaceutical products, packaging for personal care products, and others (Pareek et al., 2014).

Non-sterile suspensions are typically prepared using soda lime and borosilicate glass. In cases where light is the main factor contributing to a product's deterioration, amber coloured glass is sometimes the best choice. Unwanted ultraviolet light cannot flow through amber glass. Glass can be made to exhibit amber qualities by adding various chemicals (Gahleitneret al., 2019).

Advantages of Glass materials

- It is transparent.
- It is available in various shapes and size.
- Protect the materials from photosensation.
- It has good protection power.
- It can be easily labelled.
- It does not decay with age.

Four type of glass used in packaging industry

- **Type I-Borosilicate glass**
  Glass is extremely durable and chemically inert. Glass's alkali and earth cations are substituted out for boron, aluminium, and/or zinc. These are used to store potent alkalis and acids.
- **Type 2-Treated soda-lime glass**
  Compared to Type I glass, these are more chemically inert. "Sulphur treatment" de-alkalizes the glass surface to stop blooming/weathering on bottles.
- **Type III- Regular soda lime glass**
  Glass made of soda and lime that has moderate chemical resistance.
- **Type IV- General Purpose soda lime glass**
  Glass is only used for products meant to be applied topically or orally; it is not utilised for parenteral. Ultraviolet rays are blocked by coloured glass, which effectively shields contents from light. For this, amber glass and red glass are both employed (Pareek et al., 2014).

- **Plastic**

Mostly plastic is used during packaging of oral suspension due to following reason

- **Durability**
  The lengthy polymer chains that make up the raw material for plastics make it incredibly difficult to break.
- **Safety**
  When dropped, plastic container is unbreakable and does not break into potentially harmful pieces.
- **Hygiene**
  Plastic packaging is great for the packaging of meals, medications, and pharmaceuticals since it promotes hygiene. Without the need for human assistance, it can be filled and sealed. All national and European Union food safety laws are complied with by the materials used, including the additives and raw ingredients for plastics. Products made of plastic are frequently employed in close proximity to bodily tissue as medical devices and adhere to the greatest safety standards in their life-saving applications.
- **Security**
  Tamper-evident and child-resistant closures can be utilised to create and use plastic packaging. Users can check the goods' condition before buying thanks to the pack's openness.

- **Light Weight**
  The packing materials made of plastic are strong while being lightweight. As a result, consumers and employees working in the distribution chain may easily lift and handle products that are packaged in plastic.
- **Design Freedom**
  An endless variety of pack forms and configurations can be produced because to the qualities of the materials and the wide range of processing processes used in the sector, from injection and blow moulding to thermoforming. Additionally, the wide variety of colour options and simplicity of printing and design make it easier for customers to recognise and learn about a company (de la Caba et al., 2019).

Plastic containers are made from following polymers

- **Polyethylene**
  It is a strong barrier against moisture, but a weak one against gases like oxygen. High density polyethylene is employed, and depending on the density of the polymer used, the container has four main characteristics: stiffness, moisture vapour transmission, stress cracking, and clarity or translucency (Romani et al., 2020).

- **Polypropylene**
  Polypropylene shares characteristics with polyethylene; however it also never experiences stress cracking. The packaging is softened using hot aromatic or halogenated solvents. Due to its high melting point, it can be used to sterilise items and boilable packaging. One of its main drawbacks is that it is brittle at low temperatures (Zehetmeyer et al., 2012).

- **Polyvinyl Chloride**
  It is possible to develop materials with pristine purity, strong gaseous barriers, and rigidity. Reducing the amount of leftover vinyl chloride monomers further improved the quality of PVC. Glass bottles are coated with PVC to provide a shatter-resistant covering.

- **Polystyrene**
  Rigid plastic that is transparent. High water and gaseous permeability, as well as ease of stretching and breaking, are all characteristics of polystyrene. Acrylic and rubber compounds are mixed with polystyrene to boost its permeability and strength. These are divided into three categories based on composition: moderate impact, high impact, and super impact packages (Pareek et al., 2014).

- **Nylon**
  Numerous combinations of dibasic acids and amines result in a wide range of nylon variants. Because of its strength and difficulty to mechanically break, nylon is a very durable material. Only somewhat permeable to water vapour, nylon offers resistance to a wide range of acids and alkalis. However, this drawback can also be overcome by coating the container in PE. Not suitable for long-term product storage (Lau et al., 2000).

- **Polycarbonate**
  Has the capacity to be repeatedly sterilised. It is extremely stiff and might take the place of glass, vials, and syringes. It possesses attributes like high transparency, resilience to heat and flame, high dimensional stability, high impact strength, strain resistance, low water absorption, and resistance to strain. The impact strength of polycarbonates is five times greater than that of any other typical packaging plastic.

- **Acrylic multipolymers**
  These are acrylonitrile or methacrylonitrile monomer-based polymers. These allow for the packaging of goods that aren't often packaged because to its strong construction, high gas barrier, and chemical resistance (Pareek et al., 2014).

- **Polyethylene terephthalate**
  Terepthalic acid or dimethyl terepthalic acid reacts with ethylene glycol to produce an condensation polymer. Its superior strength and ability to act as a barrier for gas and odour make it a practical container for cosmetics, mouthwashes, and other goods (Mutsuga et al., 2005).

FDA regulations for packaging

FDA must be completely convinced that a medicine's packaging will maintain the drug's efficacy as well as its purity, identity, strength, and quality for the duration of its shelf life while evaluating a drug.

Only the material used in the container is approved by the FDA, not the container itself. The FDA has produced a list of substances that are "Generally Recognized as Safe" (GRAS). According to knowledgeable specialists, they are secure under typical circumstances. The maker must assess the substance to determine whether it falls under this category (GRAS), and data must be reported to FDA. "Container, closure, and other components of the package must not be reactive, additive or absorbing to drug," according to the specific FDA regulation for the medication (Pauli et al., 1995).

Labelling in oral suspensions

The term "labelling" refers to any printed, stencilled marked, embossed or impressed text or graphic matter on the immediate container, the outer pack, and any additional printed materials given with the pharmaceutical product. These labelling recommendations must be used in accordance with “Part VIII” of the Medicines Regulations (Tong et al., 2014).

Storage requirements of suspension

- Shake well before use.
- Do not deep freez.
- Protected from light (In case of light sensitive drugs).

Conclusion

Oral suspension shows high level of acceptance in case of administration of dosage form and its patient compliance. Due the stability and ability of masking the unpleasant taste of drugs substances oral suspension is convenient route of drug delivery.

References

1) Kulshreshtha, A.K., Singh, O.N. and Wall, G.M. eds., 2009. *Pharmaceutical suspensions: from formulation development to manufacturing*. Springer Science & Business Media.
2) Goins, R.A., Ascher, D., Waecker, N., Arnold, J. and Moorefield, E., 2002. Comparison of fluconazole and nystatin oral suspensions for treatment of oral candidiasis in infants. *The Pediatric infectious disease journal*, *21*(12), pp.1165-1167.
3) Nahata, M.C., 1999. Development of two stable oral suspensions for gabapentin. *Pediatric neurology*, *20*(3), pp.195-197.
4) Grießmann, K., Brietkreutz, J., Schubert-Zsilavecz, M. and Abdel-Tawab, M., 2007. Dosing accuracy of measuring devices provided with antibiotic oral suspensions. *Paediatric and Perinatal Drug Therapy*, *8*(2), p.61.
5) Dickinson, E., 2003. Hydrocolloids at interfaces and the influence on the properties of dispersed systems. *Food hydrocolloids*, *17*(1), pp.25-39.
6) Matveenko, V.N. and Kirsanov, E.A., 2011. The viscosity and structure of dispersed systems. *Moscow University Chemistry Bulletin*, *66*(4), pp.199-228.
7) Viveksarathi, K., Rajarajan, R., Kannan, K. and Manavalan, R., 2012. Dosage form design and evaluation of eperisone hydrochloride matrix film coated extended release tablets. *Int J Pharm Pharm Sci*, *4*(2), pp.575-581.
8) Pharmacopoeia, I., 1996. Ministry of health and family welfare, Govt. of India. *controller of publications, New Delhi*, *736*, pp.A80-83.
9) Kumar, R.S. and Yagnesh, T.N.S., 2016. Pharmaceutical suspensions: patient compliance oral dosage forms. *World Journal of Pharmacy and Pharmaceutical Sciences*, *7*(12), pp.1471-1537.
10) Pons, V., Greenspan, D., Lozada-Nur, F., McPhail, L., Gallant, J.E., Tunkel, A., Johnson, C.C., McCarty, J., Panzer, H., Levenstein, M. and Barranco, A., 1997. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. *Clinical infectious diseases*, *24*(6), pp.1204-1207.

11) Bardeskar, C. and Geeverghese, R., 2014. Reconstitutable oral suspensions (dry syrups): An overview. *World Journal of Pharmaceutical Research*, *4*(3), pp.462-484.
12) Bruns, C. and Ober, M., 2018. Development and Preparation of Oral Suspensions for Paediatric Patients–a Challenge for Pharmacists. *Pharmaceutical Technology in Hospital Pharmacy*, *3*(2), pp.113-119.
13) Ribeiro, A.M., Figueiras, A. and Veiga, F., 2015. Improvements in topical ocular drug delivery systems: hydrogels and contact lenses. *Journal of Pharmacy & Pharmaceutical Sciences*, *18*(5), pp.683-695.
14) Pabst, W., 2004. Fundamental considerations on suspension rheology. *CERAMICS SILIKATY.*, *48*(1), pp.6-13.
15) Weiner, N., 1986. Strategies for formulation and evaluation of emulsions and suspensions: Some thermodynamic considerations. *Drug Development and Industrial Pharmacy*, *12*(7), pp.933-951.
16) Gallardo, V., Zurita, L., Ontiveros, A. and Durán, J.D.G., 2000. Interfacial properties of barium sulfate suspensions. Implications in their stability. *Journal of pharmaceutical sciences*, *89*(9), pp.1134-1142.
17) Garcell, L., Morales, M.P., Andres-Verges, M., Tartaj, P. and Serna, C.J., 1998. Interfacial and rheological characteristics of maghemite aqueous suspensions. *Journal of Colloid and Interface science*, *205*(2), pp.470-475.
18) Osorio, F., Valdés, G., Skurtys, O., Andrade, R., Villalobos-Carvajal, R., Silva-Weiss, A., Silva-Vera, W., Giménez, B., Zamorano, M. and Lopez, J., 2017. Surface free energy utilization to evaluate wettability of hydrocolloid suspension on different vegetable epicarps. *Coatings*, *8*(1), p.16.
19) Reiner, E.S. and Radke, C.J., 1990. Variational approach to the electrostatic free energy in charged colloidal suspensions: general theory for open systems. *Journal of the Chemical Society, Faraday Transactions*, *86*(23), pp.3901-3912.
20) Hansen, J.P. and Löwen, H., 2000. Effective interactions between electric double layers. *Annual Review of Physical Chemistry*, *51*(1), pp.209-242.
21) Hou, T., Xu, R., Tiwari, D. and Zhao, A., 2007. Interaction between electrical double layers of soil colloids and Fe/Al oxides in suspensions. *Journal of Colloid and Interface Science*, *310*(2), pp.670-674.
22) Larsson, M., Hill, A. and Duffy, J., 2012. Suspension stability; why particle size, zeta potential and rheology are important. *Annual transactions of the Nordic rheology society*, *20*(2012), p.6.
23) Júnior, J.A.A. and Baldo, J.B., 2014. The behavior of zeta potential of silica suspensions. *New Journal of Glass and Ceramics*, *4*(02), p.29.
24) Greenwood, R., 2003. Review of the measurement of zeta potentials in concentrated aqueous suspensions using electroacoustics. *Advances in Colloid and Interface Science*, *106*(1-3), pp.55-81.
25) Bossler, F. and Koos, E., 2016. Structure of particle networks in capillary suspensions with wetting and nonwetting fluids. *Langmuir*, *32*(6), pp.1489-1501.
26) Sun, Y.Q. and Gao, T., 2002. The optimum wetting angle for the stabilization of liquid-metal foams by ceramic particles: Experimental simulations. *Metallurgical and Materials Transactions A*, *33*(10), pp.3285-3292.
27) Ninham, B.W., 1999. On progress in forces since the DLVO theory. *Advances in colloid and interface science*, *83*(1-3), pp.1-17.
28) Trefalt, G. and Borkovec, M., 2014. Overview of DLVO theory.
29) Adamczyk, Z. and Weroński, P., 1999. Application of the DLVO theory for particle deposition problems. *Advances in colloid and interface science*, *83*(1-3), pp.137-226.
30) Gregory, J. and O'Melia, C.R., 1989. Fundamentals of flocculation. *Critical Reviews in Environmental Science and Technology*, *19*(3), pp.185-230.
31) Bratby, J., 1980. Coagulation and flocculation. *Uplands: Croydon, England*.
32) Landrou, G., Brumaud, C. and Habert, G., 2018. Influence of magnesium on deflocculated kaolinite suspension: Mechanism and kinetic control. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *544*, pp.196-204.
33) Sutherland, I.W., 1991. Alginates. In *Biomaterials* (pp. 307-331). Palgrave Macmillan, London.
34) Marques-Marinho, F.D. and Vianna-Soares, C.D., 2013. Cellulose and its derivatives use in the pharmaceutical compounding practice. In *Cellulose-Medical, Pharmaceutical and Electronic Applications*. IntechOpen.
35) Abu-Jdayil, B. and Ghannam, M., 2014. The modification of rheological properties of sodium bentonite-water dispersions with low viscosity CMC polymer effect. *Energy Sources, Part A: Recovery, Utilization, and Environmental Effects*, *36*(10), pp.1037-1048.
36) Guo, J.H., Skinner, G.W., Harcum, W.W. and Barnum, P.E., 1998. Pharmaceutical applications of naturally occurring water-soluble polymers. *Pharmaceutical science & technology today*, *1*(6), pp.254-261.

37) Rahman, M.S., Hasan, M.S., Nitai, A.S., Nam, S., Karmakar, A.K., Ahsan, M.S., Shiddiky, M.J. and Ahmed, M.B., 2021. Recent developments of carboxymethyl cellulose. *Polymers*, *13*(8), p.1345.
38) Varshney, V.K., Gupta, P.K., Naithani, S., Khullar, R., Bhatt, A. and Soni, P.L., 2006. Carboxymethylation of α-cellulose isolated from Lantana camara with respect to degree of substitution and rheological behavior. *Carbohydrate polymers*, *63*(1), pp.40-45.
39) Solberg, H.F., 1977. *Hydrocyclone efficiency* (Doctoral dissertation, University of British Columbia).
40) Battista, O.A. and Smith, P.A., 1962. Microcrystalline cellulose. *Industrial & Engineering Chemistry*, *54*(9), pp.20-29.
41) Azani, N.F.S.M., Haafiz, M.M., Zahari, A., Poinsignon, S., Brosse, N. and Hussin, M.H., 2020. Preparation and characterizations of oil palm fronds cellulose nanocrystal (OPF-CNC) as reinforcing filler in epoxy-Zn rich coating for mild steel corrosion protection. *International journal of biological macromolecules*, *153*, pp.385-398.
42) Femi-Oyewo, M.N., Adedokun, M.O. and Olusoga, T.O., 2004. Evaluation of the suspending properties of Abizia zygia gum on sulphadimidine suspension. *Tropical journal of pharmaceutical Research*, *3*(1), pp.279-284.
43) Kulkarni, V.S. and Shaw, C., 2015. *Essential chemistry for formulators of semisolid and liquid dosages*. Academic Press.
44) Nejatian, M., Abbasi, S. and Azarikia, F., 2020. Gum Tragacanth: Structure, characteristics and applications in foods. *International Journal of Biological Macromolecules*, *160*, pp.846-860.
45) Emam-Djomeh, Z., Fathi, M. and Askari, G., 2019. Gum Tragacanth (Astragalus gummifer Labillardiere). *Emerging Natural Hydrocolloids: Rheology and Functions*, pp.299-326.
46) Eraga, S.O., Iwuagwu, M.A. and Adikwu, M.U., 2014. Evaluation of the suspending properties of the coprecipitate of Irvingia gabonesis gum and gelatin. *Tropical Journal of Pharmaceutical Research*, *13*(6), pp.843-848.
47) Harsha, S., 2013. Pharmaceutical suspension containing both immediate/sustained-release amoxicillin-loaded gelatin nanoparticles: preparation and in vitro characterization. *Drug design, development and therapy*, *7*, p.1027.
48) Karnok, K.J., Xia, K. and Tucker, K.A., 2004. Wetting agents: What are they, and how do they work. *Golf Course Management*, *72*(6), pp.84-86.
49) Brostow, W., Pal, S. and Singh, R.P., 2007. A model of flocculation. *Materials Letters*, *61*(22), pp.4381-4384.
50) Taylor, N.W. and Bagley, E.B., 1974. Dispersions or solutions? A mechanism for certain thickening agents. *Journal of Applied Polymer Science*, *18*(9), pp.2747-2761.
51) Aliabadi HM, Romanick M, Desai S, Lavasanifar A. Effect of buffer and antioxidant on stability of a mercaptopurine suspension. American Journal of Health-System Pharmacy. 2008 Mar 1;65(5):441-7.
52) Mark, H.F., 2013. *Encyclopedia of polymer science and technology, concise*. John Wiley & Sons.
53) Šuleková, M., Smrčová, M., Hudák, A., Heželová, M. and Fedorová, M., 2017. Organic colouring agents in the pharmaceutical industry. *Folia Vet*, *61*(3), pp.32-46.
54) Sengupta, A. and Sarkar, A., 2021. Green synthesis of nanoparticles: prospect for sustainable efficient photocatalytic dye degradation. In *Photocatalytic Degradation of Dyes* (pp. 405-420). Elsevier.
55) Ghorpade SB, Bhoyar SK. In Process & Finished Products Quality Control.
56) Shirisha, V., Ghosh, S., Rajni, B. and Banji, D., 2014. An Updated Review on IPQC Tests for Sterile and Non Sterile Products. *Research Journal of Pharmacy and Technology*, *7*(2), pp.255-265.
57) Lockhart, H. and Paine, F.A., 1996. *Packaging of pharmaceuticals and healthcare products*. Springer Science & Business Media.
58) Gahleitner, M., Tranninger, C. and Doshev, P., 2019. Polypropylene copolymers. In *Polypropylene Handbook* (pp. 295-355). Springer, Cham.
59) Pareek, V.I.K.A.S. and Khunteta, A., 2014. Pharmaceutical packaging: current trends and future. *Int J Pharm Pharm Sci*, *6*(6), pp.480-485.
60) de la Caba, K., Guerrero, P., Trung, T.S., Cruz-Romero, M., Kerry, J.P., Fluhr, J., Maurer, M., Kruijssen, F., Albalat, A., Bunting, S. and Burt, S., 2019. From seafood waste to active seafood packaging: An emerging opportunity of the circular economy. *Journal of cleaner production*, *208*, pp.86-98.
61) Romani, V.P., Martins, V.G. and Goddard, J.M., 2020. Radical scavenging polyethylene films as antioxidant active packaging materials. *Food Control*, *109*, p.106946.
62) Zehetmeyer, G., Soares, R., Brandelli, A., Mauler, R.S. and Oliveira, R.V., 2012. Evaluation of polypropylene/montmorillonite nanocomposites as food packaging material. *Polymer bulletin*, *68*(8), pp.2199-2217.

63) Lau, O.W. and Wong, S.K., 2000. Contamination in food from packaging material. *Journal of chromatography A*, *882*(1-2), pp.255-270.
64) Mutsuga, M., Tojima, T., Kawamura, Y. and Tanamoto, K., 2005. Survey of formaldehyde, acetaldehyde and oligomers in polyethylene terephthalate food-packaging materials. *Food Additives and contaminants*, *22*(8), pp.783-789.
65) Pauli, G.H. and Tarantino, L.M., 1995. FDA regulatory aspects of food irradiation. *Journal of food protection*, *58*(2), pp.209-212.
66) Tong, V., Raynor, D.K. and Aslani, P., 2014. Design and comprehensibility of over-the-counter product labels and leaflets: a narrative review. *International Journal of Clinical Pharmacy*, *36*(5), pp.865-872.